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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,911	06/07/2006	Naoka Kida	Q95279	8940

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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,911	KIDA ET AL.	
	Examiner	Art Unit	
	Thane Underdahl	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

Claims 1-9 received on 6/7/06 are pending in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim states "a 5-cm RWV vessel is used". This phrase is indefinite since it does not teach what dimension of the vessel is 5 cm. Clarification is required. In the interest of compact prosecution, the claim will read as "a 5 cm diameter RWV vessel is used".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Goodwin et al. (U.S. Patent # 5,496,722, 1996) and Schwarz et al. (U.S. Patent # 5,026,650, 1991) with support from Unsworth et al. (Nature Medicine, 1998). The reason why two references are cited for this 35 U.S.C § 102(b) rejection is that Goodwin

et al. expressly incorporates the patent of Schwartz et al. in their application (Goodwin et al., col 8, lines 5-10). M.P.E.P. § 2163.07(b) states:

> "Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed."

Therefore it is proper to include the information of the incorporated reference as if it were included in the parent document and as such treated as if it were the same document when applied against the current claims.

These claims are drawn to a method grow bone marrow cells into a three-dimensional (**3D**) tissue in a simulated microgravity environment. Claim 2 limits the gravity to 10^{-1} to 10^{-2} of ground gravity on a time average basis. This microgravity is achieved using a uniaxial rotary bioreactor such as a Rotating Wall Vessel (**RWV**). Claim 9 limits that the bone marrow cells are isolated from a subject in need of transplantation of the engineered cartilage tissue.

Goodwin et al. teach a method of culturing bone marrow cells in a 3D into a tissue in a simulated microgravity environment (Goodwin et al. col 4, lines 36-45). This microgravity environment is simulated by a RWV (Goodwin col 8, lines 5-10) which compensates ground gravity with the stress of the rotating vessel (Schwarz, col 6, lines 5-15). RWVs simulate an environment of 10^{-2} of ground gravity as supported by Unsworth et al.(Unsworth et al., page 902, col 1). Goodwin et al. further teach that bone marrow can be obtained from the

patient, tissue grown and then transplanted back to the patient (Goodwin col 5, lines 5-12). Therefore the reference anticipates claims 1-5 and 9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9.

The description and rejection of claims 1-5 and 9 are described in the 35 U.S.C § 102(b) rejection above. Claim 8 limits that the bone marrow cells of claim 1 must be two-dimensionally cultured to confluence, subcultured and then cultured in a simulated microgravity environment.

Goodwin et al. teach their 3D bone marrow tissue is bone marrow cells (col 6, lines 35-45). Goodwin et al. also teach that bone marrow cells are cultured in a 2D culture (col 4, lines 20-25). Goodwin et al. also teach that "In the case of preparing bone marrow for recipients volumes are expanded as cellular densities or metabolic requirements dictate. The limited parameters may depend on the rotating vessel's ability to suspend large aggregates" (col 14, lines 25-34). One of ordinary skill in the art would recognize that this is a form of sub-culturing cellular bone marrow cells before being added to the RWV and that the "aggregates" of bone marrow Goodwin is referring

to are confluent tissues of bone marrow cells. Goodwin et al. also teaches that 2D bone marrow cell cultures have a decreased production over time (col 4, lines 20-25). It would have been obvious to someone skilled in the art to start the bone marrow culture from the primary cells then transfer it to a 2D culture flask to produce bone a marrow monolayer for aggregates that can be cultured in a RWV. One of ordinary skill in the art would recognize that culturing a monolayer of bone marrow is to confluence. The motivation is provided by Goodwin et al. who state that while it is possible to culture bone marrow monolayers in 2D the bone marrow cell production decreases over time (col 4, lines 20-25). Therefore if Goodwin et al. desires an expansion of the bone marrow cells, it would be obvious to culture the aggregates from a 2D monolayer in a microgravity environment where Goodwin et al. has shown reasonable expectation of success by achieving high cell densities in a 3D structure. Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-5, 8 and 9 are not allowable.

Claims 1-6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9 above, and further in view of Synthecon (http:/synthecon.com/products.shtml, available Feb 5, 2002 as verified by web.archive.org).

The description and rejection of claims 1-5 and 9 are described in the 35 U.S.C § 102(b) rejection above. Claim 6 further limits claim 5 by teaching the bone marrow be cultured by seeding the cells as a density of 10^6 to 10^7 cells/cm^3 at a rotational speed of 8.5 to 25 rpm when a 5 cm diameter RWV vessel is used. Goodwin et al. teach that

bone marrow cells are added to the RWV at a concentration of $1X10^6$ cells/cm^3 (Goodwin et al., col 13 lines 59-63). Schwarz et al. teach that the RWV rotates at 10 rpm (Schwarz et al., col 6, lines 35-40). While neither of the art listed above teaches that the RWV has a 5 cm diameter vessel this would be obvious to one of ordinary skill in the art at the time the invention was made in view of Synthecon.

Synthecon teach that RWV culture systems can be made to almost any size required by the experimenter without affecting the physics of the system (Synthecon, page 2). Absent any teaching of criticality by the applicant concerning the dimensions of the RWV listed in claim 6 it would be *prima facie* obvious that one of ordinary skill in the art would recognize that the size of the RWV vessel in claim 6 is a result effective variable that depends on the size of the culture required by the experimenter, which is a matter of routine optimization (M.P.E.P. § 2144.05 II). Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-6 and 9 are not allowable.

Claims 1-5, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9 above, and further in view of Yan et al. (U. S. Patent Application Publication # 2002/0168763) and Simpson et al. (U. S. Patent Application Publication # 2002/0090725). The description and rejection of claims 1-5 and 9 are described in the 35 U.S.C § 102(b) rejection above. Claim 7 further limits the method of claim 1 by requiring TGF- β and/or dexamethasone in the culture medium.

While Goodwin et al. teach that "various growth factors" may be added to the culture medium to "emulate *in situ* conditions" (Goodwin, col 4, lines 3-5). While Goodwin et al. does not specifically teach TGF- β this would be obvious to one of ordinary skill in the art at the time the invention was made in view of Simpson et al. who teach the addition of TGF- β to the culture medium (Simpson et al., paragraph 98) to grow collagen matrices in a microgravity reactor (Simpson et al., paragraph 207) that contain cells from bone marrow (Simpson et al., paragraph 204). It would have been obvious to someone skilled in the art to modify the invention of Goodwin et al. with the teachings of Simpson et al. since both culture bone marrow cells in a microgravity reactor. The motivation comes from Goodwin et al. who desires to create a culture that emulates *in situ* conditions and one of ordinary skill in the are would recognize that TGF- β would be present in the body where bone marrow cells are cultured. The reasonable expectation of success is provided by Simpson et al. who teach the addition of TGF- β to the culture.

Likewise Goodwin et al. does not teach the addition of dexamethasone to their culture media, however this would be obvious at the time the invention was made in view of the teachings of Yan et al. Yan et al. teach the addition of dexamethasone to their culture media (Yan, paragraphs, 178 and 330) that grows bone marrow cells (Yan, paragraph 85) in a microgravity environment (Yan, paragraph 111) for bone marrow transplantation (Yan, paragraph 43) which is the same purpose as Goodwin et al. It would have been obvious to someone

skilled in the art to add dexamethasone to the culture medium since Yan et al. and Goodwin et al. share the same purpose, see M.P.E.P. § 2144.06.

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-5, 7 and 9 are not allowable.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached during regular business hours, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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